OXIDATIVE METABOLISM OF NICOTINE *IN VIVO*

Peyton Jacob, III, Ph.D.
University of California, San Francisco
San Francisco General Hospital, Building 100, Room 235
1001 Potrero Avenue
San Francisco, California 94110

Nicotine undergoes a variety of metabolic reactions involving oxidation, most of which result in transformations of the pyrrolidine ring. The major route of metabolism in most mammalian species involves oxidation of the 5'-carbon atom to give the γ-lactam derivative cotinine. Oxidation of the N-methyl group results in demethylation to nornicotine, which is a minor metabolite in humans. Nicotine also undergoes oxidation of the pyrrolidine nitrogen atom to give a diasteriomeric mixture of N-oxides. Cotinine is extensively metabolized in humans, with only 10-20% being excreted unchanged in urine. It appears that the major urinary metabolite of cotinine is trans-3'-hydroxycotinine which results from oxidation adjacent to the carbonyl. Formation of this metabolite in humans has been shown to be highly stereoselective. Cotinine is also metabolized by N-oxidation of the pyridine nitrogen atom, but cotinine N-oxide is a minor metabolite in humans, accounting for only a few percent of the nicotine absorbed by smokers. Other metabolites resulting from oxidative degradation of the pyrrolidine ring have been reported, but the pathways by which they are formed are not well understood, and their quantitative importance in humans is unknown.

In this paper the various oxidative pathways will be discussed, with emphasis on quantitative and stereochemical aspects of nicotine metabolism in humans. Applications of metabolic data in clinical pharmacologic studies will also be discussed.